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Investigation of the function of the corpus striatum.

by

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Final Technical Report

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The final year under the contract on investigation of the function of the corpus striatum has been devoted to preparation of:

- 1) A review entitled "Corpus striatum"
- 2) A manuscript entitled "Conditioned avoidance behavior of cats with lesions in the globus pallidus",

and to investigations of:

- 3) Learning in cats with lesions in the globus pallidus
- 4) The ability of pigeons to discriminate between other pigeons.

1) The investigations done in this laboratory under the contract and recent work in other laboratories have fundamentally changed our views of the function of the corpus striatum. The subject is furthermore of interest because lesions placed in the globus pallidus have become a treatment for Parkinson's disease during the past ten years. The review covers research on the subject since it was reviewed by Rioch (1940) and discussed in a symposium (Putnam 1942). It is concerned with animal experiments in physiology, anatomy, psychology and biochemistry. Clinicopathological deductions about the function of the corpus striatum were reviewed recently by Jung and Hassler (1960) and Denny-Brown (1962). The review (110 pages in print) has been accepted for publication as a supplement to the *Acta physiologica scandinavica*. It contains chapters on:

The "extrapyramidal system"

Motor function

Histology

Electrical signs of connections between the corpus striatum and other parts of the brain

Sensory function

Behavioral studies

Biochemical studies

Pallido-ansotomy in humans

ACTA

In general it can be summarized as follows:

Previous concepts.

Systematic investigation of the corpus striatum began with Magendie (1839). Neither he nor Ferrier (1880) distinguished between the grey substance of the caudate nucleus, putamen and globus pallidus and the white substance of the internal capsule. A contralateral paresis was produced when these structures were destroyed; stimulation elicited flexion movements of contralateral extremities. Bilateral ablation of the corpus striatum produced running forwards; running backwards occurred after ablation of the cerebellum.

The next period (1880-1910) was characterized by attempts to sort out the functions of the corpus striatum from those of the internal capsule. The main results were that movements could not be elicited by electrical stimulation of the caudate nucleus when the internal capsule had degenerated and that motor defects were absent after lesions confined to the caudate nucleus. Nor could effects on the autonomic nervous system, which had been attributed to the corpus striatum, be confirmed. Solely globus pallidus was believed to have motor function, since electrical stimulation of it evoked convulsions even when the internal capsule had degenerated (Bechterew 1909). Ideas about the function of the corpus striatum changed completely in the clinicopathological epoch initiated by Cecile Vogt (1911) and Wilson (1912). They described the syndrome of the corpus striatum characterized by involuntary movements and disturbances in muscle tone without defects in sensation and intelligence. Since the internal capsule ("pyramidal tract") was intact in patients with the syndrome of the corpus striatum, Wilson stated that: "It is unfortunate that there is no expression in common use to indicate extrapyramidal motor disease". However, matters were more complicated than originally assumed because regions outside the corpus striatum were damaged as well in cases resembling Vogt's and Wilson's syndrome in other respects. These different regions together with the corpus striatum were

thought to be an interconnected, integrated motor system called the striatal system by Vogt and Vogt (1919, 1920) and the extrapyramidal system by Jacob (1923).

The clinicopathological observations led to attempts to deduce the pathophysiology of involuntary movements and rigidity and to speculations about the normal physiology of the "striatal" or "extrapyramidal" system. The corpus striatum was believed to inhibit brain regions directly concerned with movement; abnormal involuntary movements were attributed to release from "striatal" inhibition. Autopsy findings were interpreted to indicate that the corpus striatum was a center of automatic and instinctive movements, associated movements etc. (Jacob 1923).

In the nineteen-forties concepts of the function of the corpus striatum were again based on animal experiments. Inhibition of movements was elicited by stimulation through electrodes placed in the corpus striatum (Mettler et al. 1939) and strychnine neurography led Dusser de Barenne and McCulloch (1938) to suggest a suppressor circuit: area 4s → nucleus caudatus → globus pallidus → thalamus → area 4. These findings were consistent with clinicopathological conclusions and were the basis of new ideas about the mechanism of tremor and choreo-athetosis (Bucy 1942).

Present concept.

The idea of the suppressor circuit has been abandoned; the suppression described by Dusser de Barenne and McCulloch resembled the "spreading depression" of Leão (1944). Inhibition of movement is due to spread of current to the internal capsule in anesthetized (Peacock 1954) as well as in alert cats (Laurson 1962 b).

There is no anatomical evidence to indicate direct projections from the caudate nucleus to the cerebral cortex (Voneida 1960, Szabo 1962). The results of electrical stimulation and recording have been interpreted to indicate direct and indirect connections between the caudate nucleus and cerebral cortex. Precautions to detect spread of current to the structures surrounding the caudate nucleus indicate, however, that cortical responses to stimulation of the caudate nucleus are absent. Previous findings may be attributed to spread of current to either the corpus callosum, internal capsule or tha-

lamus. Similarly, electrocortical arousal is absent after stimulation confined to the caudate nucleus; corpus striatum is not a part of the reticular activating system (Laursen 1961 a, b).

On the other hand there is anatomical evidence that the cerebral cortex projects to the corpus striatum, and single units in the caudate nucleus discharge in response to stimulation of the cortex (Albe-Fessard et al. 1960 b, Laursen 1961 a).

Sensory stimuli of different modalities evoke responses of single units in the corpus striatum. Stimulation of the caudate nucleus evokes turning of the head to the contralateral side and running in circles as if the cat were searching for something. Stereotyped flexion movements of contralateral extremities, elicited through electrodes in the caudate nucleus, can be attributed to excitation of the internal capsule (Laursen 1962 a).

Lesions in the caudate nucleus reduce a monkey's ability to remember whether or not food is placed in a covered cup (Battig, Rosvold and Mishkin 1960). Lesions in the globus pallidus produce rapid extinction of conditioned avoidance responses in cats at a time after the operation when retention of the response has returned to normal; this indicates diminished fear (Laursen 1962 d).

The function of the corpus striatum is on a high level of integration.

2) A manuscript entitled "Conditioned avoidance behavior of cats with lesions in globus pallidus" has been accepted for publication in *Acta physiologica scandinavica*. The initial phases of the study were summarized in last year's final technical report together with some preliminary results. After analysis and statistical treatment of the results it can be concluded that after both unilateral and bilateral lesions in globus pallidus conditioned avoidance responses were extinguished more rapidly than in normal and control operated cats. This was observed at a time when retention had returned to normal. Animals with bilateral lesions in globus pallidus tested 30 days after the operation

learned the avoidance response slower than normal and control operated cats. Retention tested 30 days after bilateral lesions in globus pallidus was impaired as compared with normal and control operated cats. Sixty days postoperatively retention was normal. Therefore a memory defect cannot account for the rapid extinction observed more than 60 days postoperatively; it may be explained by diminished fear of a stimulus warning of a shock. The slow postoperative recovery may be due to a temporary metabolic defect. That retention of avoidance responses had returned to normal while fear still seemed to be diminished supports Brady et al.'s (1954) suggestion that retention is not dependent on fear. That retention was found normal may, however, reflect only the experimental design; more sensitive measures of retention might have shown a lasting defect. The results can be interpreted without assuming that learning or memory in general were deranged nor do they exclude that globus pallidus has other than emotional functions.

During training the avoidance latency became shorter and less variable. In unoperated cats the mean avoidance latency on the two criterion days was 4.9 ± 0.3 sec (14 cats, 36-40 trials each). Cats with bilateral lesions in globus pallidus responded with a 25 per cent longer latency (6 cats, 36-40 trials each). The slow response was not due to a motor handicap: the mean escape latency was 2.4 ± 0.2 sec (6 cats, 525 trials) in operated, 2.3 ± 0.2 sec (14 cats, 628 trials) in unoperated cats.

3) The experiments reported above can be interpreted by assuming that reduced fear is the only lasting change induced by bilateral lesions in the globus pallidus. But other changes are probably produced as well since the globus pallidus has widespread connections. Various experiments are planned to explore these possible changes and the series under way is designed to determine whether learning factors other than motivation are deranged at a time after bilateral lesions in the globus pallidus when the cats

appear normal.

Above each of two levers is a light bulb and a cat is trained to press the lever indicated by the strongest light to get food. When the cat presses the lever with the weakest light, i.e. makes an incorrect response, she gets a weak electric shock on the paw touching the lever. One or the other lever is correct in a random sequence, controlled automatically with relays and switches. The difference in brightness between the two lights is adjusted so that the cat makes 80 to 85 per cent correct responses. The shock is adjusted so that its effect is to increase the number of correct responses.

If the only change after bilateral lesions in the globus pallidus is reduced fear, the number of correct responses should still increase when incorrect responses are punished with a shock. It may be necessary to increase the strength of the shock to obtain an effect similar to that observed preoperatively. By adjusting the difference between the lights and the strength of the shock it should be possible to discern differences in the behavior of cats before and after operation and in cats with control lesions in the thalamus (centrum medianum). Preliminary results suggest that it may be possible by this method to detect a changed "learning variable" in a situation where motivation is changed and to express these changes as relative quantities. A number of cats are at different stages of training.

4) Last year we reported the initial stages of a study of the ability of pigeons to discriminate other pigeons. The study is based on previous experiences with the effect of lesions in the corpus striatum on the sexual behavior.

Discrimination is investigated in a modified Skinner box. A pigeon is trained to peck on one key (a) when a pigeon (A) is presented and to peck on another key (b) when another pigeon (B) is presented. The "stimulus" pigeons (A) and (B) are presented in a random sequence and social interaction with the discriminating

(key pecking) pigeon is prevented by a one way window. Correct responses (key (a) to pigeon (A) or key (b) to pigeon (B)) are reinforced with food, incorrect responses (key (b) to pigeon (A) or key (a) to pigeon (B)) are punished by 15 seconds of darkness. The discriminating pigeon is first taught to use the box with an easy task, i.e. the objects to discriminate are cards with horizontal or vertical stripes. Control experiments are necessary because pigeons have a remarkable ability to pick up "irrelevant" cues, hardly noticeable for the human. One important control experiment is to reverse the "stimulus" pigeons so that key (a) must be matched to pigeon (B) to produce food; the pigeon will make mostly "incorrect" responses if it was the pigeon, not other objects, he in fact discriminated. In time he is retrained on the task.

In the first part of the study the discriminating pigeons have been males and their task has been to discriminate between their mate and a strange female. We have found that:

- a) A male pigeon recognizes his mate even when she is presented to him motionless between boards of transparent plastic.
- b) Peculiar colors and patterns of feathers play no role in the pigeon's discrimination. Male pigeons discriminate between female pigeons which are identical to the human eye.
- c) A male most easily discriminates between females presented so that they face him. He can with difficulty (inconstantly) discriminate when the female pigeons are presented sideways, turned to the same or to opposite sides; he cannot discriminate when the females are turned with their tails towards him.
- d) The male must see the head ("face") and the upper part of the neck of the female to discriminate. The rest of the body can be covered.

It takes longer for a pigeon to learn to discriminate other pigeons than to discriminate striped cards. Either pigeon-pigeon discrimination is a difficult task when social interaction is pre-

(key pecking) pigeon is prevented by a one way window. Correct responses (key (a) to pigeon (A) or key (b) to pigeon (B)) are reinforced with food, incorrect responses (key (b) to pigeon (A) or key (a) to pigeon (B)) are punished by 15 seconds of darkness. The discriminating pigeon is first taught to use the box with an easy task, i.e. the objects to discriminate are cards with horizontal or vertical stripes. Control experiments are necessary because pigeons have a remarkable ability to pick up "irrelevant" cues, hardly noticeable for the human. One important control experiment is to reverse the "stimulus" pigeons so that key (a) must be matched to pigeon (B) to produce food; the pigeon will make mostly "incorrect" responses if it was the pigeon, not other objects, he in fact discriminated. In time he is retrained on the task.

In the first part of the study the discriminating pigeons have been males and their task has been to discriminate between their mate and a strange female. We have found that:

- a) A male pigeon recognizes his mate even when she is presented to him motionless between boards of transparent plastic.
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- d) The male must see the head ("face") and the upper part of the neck of the female to discriminate. The rest of the body can be covered.

It takes longer for a pigeon to learn to discriminate other pigeons than to discriminate striped cards. Either pigeon-pigeon discrimination is a difficult task when social interaction is pre-

vented, or the key pecking pigeon is somehow inhibited. He does not appear confused. When he is put in the box and sees the mate, he often begins the ceremonies of mating behavior. Soon, however, he begins to operate the keys for food with as many responses per minute as he makes when the task is to discriminate striped cards.

The pigeon's performance is more variable from day to day when he works on a pigeon-pigeon problem than when he works on a problem of striped cards. Sometimes there are indications of a cyclical variation with a period of about 10-12 days. We are not aware of any similar cycle in the pigeon's behavior outside the experiment.

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The personnel utilized.

During the reporting period the personnel consisted of:

Arne Mosfeldt Laursen, M.D.
 Bente Broch, technical assistant (histology)
 Thomas Nissen, student of psychology
 Edith Vinay, animal care
 Emma Nielsen, animal care
 Karen Madsen, animal care (till November 1962)
 Susanne Ifversen, animal care (from November 1962).
 The personnel of the workshop and of the electronic laboratory
 of the institute
 Fritz Buchthal, M.D.

There were no changes in the research policies.

Manhours.

Arne Mosfeldt Laursen, M.D.	2700 hours
Bente Broch	624 "
Thomas Nissen	600 "
Edith Vinay	2040 "
Emma Nielsen	1440 "
Karen Madsen	960 "
Susanne Ifversen	240 "

Materials expended Danish Kroner 16.270,73

All property acquired is expendable.

Balance.

Contract amount	Danish Kroner 58.655,00
Expenses January 1 through December 31, 1962.	<u>" " 58.522,29</u>
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